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WHAT

IS THE

Comparative Physiological and Therapeutic Action of Free Phosphorus and the Hypophosphites?

AN ESSAY:

TO WHICH

THE "MERRIT H. CASH" PRIZE WAS AWARDED

BY THE

NEW YORK STATE MEDICAL SOCIETY, 1876.

BY

SAMUEL R. PERCY, M. D.,

47 West 38th Street, New York,

Professor of Materia Medica in the New York Medical College; Professor of Materia Medica and Chemistry in the America Veterinary College; Honorary Member and late Physician to Mt. Sinai Hospital; Recipient of the Prize of the American Medical Association for the year 1863, and also for the years 1866 and 1872; Recipient of the Prize of the Alumni Association of the Medical Department of Columbia College for the year 1866, and also for the years 1867 and 1868; Recipient of the Merrit H. Cash Prize awarded by the New York State Medical Society for the year 1876.

Extracted from the Transactions of the New York State Medical Society.

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WHAT IS THE

Comparative Physiological and Therapeutic Action of Free Phosphorus and the Hypophosphites?

By SAMUEL R. PERCY, M. D., of New York.

There is probably no medicine more used at the present time than *phosphorus and its various combinations;** while one set of physicians extol the virtues of "*Free Phosphorus in Medicine*," and condemn as poisonous all the acids of phosphorus, another class claim that phosphoric acid should be used to render our bread light and nutritious, and still others, that the hypophosphites are the best of remedial agents for consumption and debility.†

I am sorry to say that a great many of the assertions made are entirely theoretical, and no attempts have been made to question these assertions by experimental facts. I am aware that Thompson has related cases of neuralgia, and other diseases that have been relieved by a certain favorite pill of "free phosphorus," of which no one knows the composition, and others have asserted that consumption can always be cured by the hypophosphites. The relation of these cases do not constitute science, nor do they give the slightest knowledge of the modus operandi of the medicine. To settle these various points of controversy, I see no other way than to analyze the observations and the related cases, test each by the known method of scientific research, and, as far as possible, give the exact modus operandi of each remedial agent.

Let me first consider a work lately published in London by J. Ashburton Thompson, "Free Phosphorus in Medicine," taking this as an exponent of the first class I have spoken of. This work has had a large circulation, and makes bolder assertions than have ever before been used. How far are they correct?

* At the present time there is no therapeutic agent making greater strides in the estimation of the profession than phosphorus.—*Lancet*, April 11th, 1874.

† Free Phosphorus in Medicine, by J. Ashburton Thompson: London, 1874. Phosphorus, its claims as a Therapeutic Agent, by Wm. M. Turner: Philadelphia, 1875. Hosford Rumford Chemical Works. Churchill on the Hypophosphites. Phosphorus as an Organismal Element, by S. Percy: New York, 1876.

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Mr. Thompson says: "Not only is the complete oxidation of phosphorus calculated to destroy its therapeutic power entirely, *but what is more serious, its imperfect oxidation, or oxidation in the lower degrees, is calculated to confer an intensity of poisonous power upon it which it does not possess in the absolutely free state.*" Again he says: "But there is good reason to believe, and the point has indeed been almost demonstrated, that some of these cases of poisoning, which occurred in the most abrupt manner, and after doses of free phosphorus which had been often given before without harm, were owing to the partial conversion of the phosphorus into hypophosphorous acid." Again: "That this conversion (of a portion of phosphorus into hypophosphorous acid) takes place in solution of phosphorus in vegetable oils, and that these solutions, thus altered, acquire poisonous properties entirely out of proportion to the amount of free element contained in them, was first noticed by Devergie, and was further noticed by Simon in his article on phosphorus. My own practical observation, and careful consideration of the facts reported by others to the effects of this solution, has led me to the conclusion that it is a dangerous preparation."

It appears, by these extracts, that Mr. Thompson considers phosphorus an active medicinal agent, but that it becomes a violently poisonous one when mingled with or held in solution by a small quantity of hypophosphorous acid; and he asserts in these extracts, and in dozens of other places through his book, that solution of phosphorus in olive oil which has not been heated becomes dangerous by the generation of hypophosphorous acid. *He gives no proof, nor does he make a single experiment to sustain these dogmatic assertions.*

Let us consider, by means of a few experiments, whether hypophosphorous acid is found in solution in ol. phosph. made with olive or almond oil which has not been heated. I have by me a solution of phosphorus in olive oil in proportion of 1 to 80, another of almond oil of the same strength: they have been made over a year, and smell quite strongly both of phosphorus and rancidity. They are both luminous and free from deposit.

EXPERIMENT 1.—Half an ounce of this olive oil solution containing three grains of phosphorus is well shaken in a small vial with an ounce of distilled water (free from air) at 100° F. The oil is allowed to settle on the top and six drams of the water are drawn off by a syphon and filtered. A solution of sulphate of copper is added, and no precipitate is formed by the application of heat. Upon boiling the liquid no hydrogen was evolved, or metallic copper set free, as would be the case if the water contained hypophosphorous acid. With the other chemical tests for this substance I discovered no hypophosphorous acid.

The same tests were applied to the solution in almond oil, with a similar result. To be satisfied on this point, I obtained half an ounce of "oleum phosphoratum" from the best druggist of this place; it had the same luminous appearance, the same phosphatic odor, but it was not so rancid. Upon applying the same tests, I met with the same negative results. A chemical friend has made thorough experiments with the same results.

Mr. Thompson is very positive that hypophosphorous acid must be formed in such oils, and reiterates, over and over again, not only that it is formed, but that it is the cause of all the uncertain and ill effects of the preparation.

It is asserted by *Graham*, and by all chemists who have written since his time, that hypophosporous acid is never produced anhydrous, but that it must have two equivalents of water associated with it as a necessary part of its composition, and that the other equivalent may be water, or it may be lime, potash, soda, forming hypophosphites. Deprive the acid of these two equivalents of water, and it is decomposed. It has no existence without water. Now, as there is no water in olive oil, I did not see how hypophosphorous acid could be formed, especially as through Mr. Thompson's whole book, he gives not a single chemical analysis to prove his numerous peculiar assertions.*

Mr. Thompson's assertions thus seem of little value. In the first place, we prove by Graham and other chemists, that hypophosphorous acid cannot so exist; in the next place, we prove by several analyses, that it does not exist.

Upon the therapeutic effects, Mr. Thompson asserts, and quotes Personne, that phosphorus is intensified in its action, and that most of its toxic effects are due to its decomposition into hypophosphorous acid, and in a case of poisoning with phosphorus, he explains it thus: "The case may be one of poisoning with an oxide or unsuspected combination of phosphorus."

Mr. Thompson, throughout his whole work, willfully shuts his eyes to any knowledge of the lower oxides of phosphorus as therapeutic agents, and looks upon them only as toxic. Dr. Churchill and innumerable other physicians, regard the lower oxides as by far the safest and best therapeutic combinations. By the mere reading of such conflicting opinions as now exist as to the comparative merits of free phosphorus and the various oxides of phosphorus, it is almost impossible to arrive at any well based conclusion, and nothing but carefully conducted experiments upon the lower animals can settle these differences.

* In the quarterly Journal of Science, Vol. VI., Dr. Graham says: "Hypophosphorous acid is colorless, rancid, and sour to the taste. The anhydrous acid has never been obtained, three equivalents of water being essential to its composition, namely, one equivalent to base, and two equivalents which form elements of the acid itself."

To arrive at truthful conclusions on these points, I have had recourse to a large number of physiological experiments, and have also searched for well-conducted experiments made by others.

I find no "Contributions to Therapeutics" of an experimental character in Mr. Thompson's book, but numerous "Contributions" by Dr. Percy, in "Phosphorus as an Organismal Element." On page 644,* he administers "free phosphorus" in a six *grain* dose, in oil, to a dog. This dog lived four days, and after death a thorough post-mortem examination was made. "Almost every muscular tissue in the body had become degenerated by oily infiltration. The intestines showed ecchymosed spots in various parts. The liver was large, of a soft doughy consistence, of a dirty brownish-yellow color, and upon the upper surface were several large ecchymosed spots. By careful mycroscopic examination, the hepatic cells were very imperfectly preserved, no distinct nucleus could be seen." "The kidneys were enlarged, soft and of an oily appearance." "Under the microscope, both cortical and medullary substance presented a broken-down mass in which nothing could be distinctly defined but oil globules." "The lungs were much collapsed; upon the pleura-pulmonalis were several reddened patches, the surface of which, when scraped off and examined under the microscope, was found to be composed of broken-down blood discs and fat globules." "The heart was enlarged, soft, and flabby." "The inner membrane of the arteries and larger veins was thickened, softened, and easily separated, smeared with oil and broken-down blood-globules."

The next experiment performed by Dr. Percy, was on a living frog, examined under the microscope after hypodermic injection of oleum phosphor. The changes which took place are fully described, *and the blood was seen to become disintegrated while circulating.*

But one of the most remarkable is Experiment 5, page 647, where six grains of phosphorus in solution in suet were given to a dog; afterwards *oxygenated* water was passed into the stomach by a tube and inhalations of *oxygen gas* were given. This dog seemed to suffer no inconvenience, and was running about the next day. He thus actually converted the phosphorus into Thompson's much dreaded "lower oxide," and saved the life of the dog.

Percy's next experiment is more conclusive still, and directly touches the point we are now discussing. Six grains of "free phosphorus" in solution in suet were given to a dog, and the toxic effects were allowed to be developed. Oxygen gas and oxygenated water were then given as in the previous case. The dog eventually recovered, but after great danger and suffering.

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*Transactions of the American Medical Association. Prize Essay. By Sam. R. Peecy, 1872.

Dr. Percy thus proved that oxygen is the true and as yet only known antidote to phosphorus poisoning, in fact that it converts the phosphorus into Mr. Thompson's dreaded poisonous lower oxide.

There are numerous experiments given in this essay upon dogs, rats, frogs, and a horse, with free phosphorus, and all with the same result—*death by fatty degeneration!*

Upon looking over these cases that have been before the profession for four years without question or refutation, it appears: 1st, That the administration of phosphorus in large doses, or repeated small doses, causes death by producing fatty degeneration of nearly all the structures of the body, and frequent ecchymosed spots; 2d, That oxygen, that seems to be dreaded so much by Mr. Thompson as being the cause of oxydation, and, consequently, of all the toxic dangers of phosphorus, was found by Dr. Percy to be the best antidote to the poisonous influence of "free phosphorus;" in fact, that it converted an active poison, phosphorus, into a mild medicine—hypophosphorous and phosphoric acids.

Dr. Percy records no experiments with hypophosphorous acid, but several with an "alkaloid hypophosphite" he manufactured. In doses of that substance, equal to half a grain of free phosphorus, continued for two days (equaling five grains of free phosphorus) a dog improved from sickness and dejection to rude health.*

As the assertions of Thompson and the recorded experiments of Percy differ so greatly, it seemed to me advisable to make some hypophosphorous acid, and see who is correct and who in error. Thompson says, *hypo*-phosphorous acid "is easily obtained by submitting the element to a limited body of air.† It is solid when anhydrous, liquid when hydrated, colorless, inodorous and very caustic."‡

I do not possess the chemical skill of Mr. Thompson. I could not make *hypo*-phosphorous acid in that way, and as Mr. Thompson gives us no formula for making this acid, I had to originate one for myself, for all the formulæ I find are so weak in acid that they would be open to objection, especially if it should be expected that Mr. Thompson's "*solid body*" should be produced.

The hypophosphorous acid I have used, I have made in the following manner: it is fully double the strength of that proposed by Proctor.

Take of hypophosphite of lime, 480 grains, crystalized oxalic acid, 350 grains, add sufficient warm distilled water to dissolve the lime salt;

* This hypophosphite of olein (first made by Professor Percy), is identical in its chemical constituents with the protagon of the brain." *C. G. Polk, M.D.*

† *Phosphorous* acid is formed by slow combustion in the atmosphere, or by burning phosphorus in a very limited supply of dry air, in which case it is anhydrous phosphorous acid." *Fowne's Chemistry*, p. 214.

‡ "There is also another oxygen acid of phosphorus containing a smaller proportion of oxygen, called hypophosphorous acid, to which there is no corresponding anhydrous oxide." *Fowne's Chemistry*, p. 214.

add, in another vessel, sufficient to dissolve the acid; mix the solutions and stir them well with a glass rod. Pour the mixture on a filter in a well prepared funnel, and wash carefully with warm distilled water until the acid is exhausted. Put aside the strong acid that first passed, in a graduated measure, evaporate the weaker acid carefully, until the whole measures 34 drams.

This is quite a concentrated solution, containing about 20 per cent. of ter-hydrated hypophosphorous acid; a dram being about equal to 12 grains of the acid, and 4½ grains of phosphorus.

PHYSICAL CHARACTERISTICS—Thompson says: "It is solid when anhydrous, liquid when hydrated, colorless, inodorous, and very caustic."

All chemists acknowledge that an anhydrous acid does not exist. I therefore did not attempt to make a solid body. The acid I made is not colorless, but of a light straw color. It is not inodorous, but possesses the marked odor of the hypophosphites. It is not caustic,* for I have had it on the back of my hand for several minutes.

EXPERIMENT 2.—I administered to a strong, healthy dog half a dram (equal to 2¼ grains of free phosphorus) of this hypophosphorous acid in two ounces of water every morning for a week. The dog was not confined, but ran about the stable. The only noticeable symptoms were, that he was more boisterous in his play, and that it acted as a powerful aphrodisiac.

EXPERIMENT 3.—To another dog I administered the same dose, and for the same length of time. In this instance the acid was shaken up in an emulsion of 2 ozs. of olive oil, daily. No ill effects followed, but he seemed unable to restrain himself from mischief. This also acted as an aphrodisiac. If these two experiments are compared with experiments 1 and 3, made by Dr. Percy in the work above mentioned,† it will be seen that 6 grains of free phosphorus produced death in from 2 to 4 days in five dogs, whereas this hypophosphorous acid, equal in quantity to 16 grains of free phosphorus, produced in a week nothing but excessive activity.

EXPERIMENT 4. –A fluid dram of this hypophosphorous acid, in its pure state, was put into the mouth of a dog, and the mouth kept closed with the hand until he swallowed it. He was allowed no water for an hour. This was repeated for three mornings. It had no caustic effect upon the mouth, nor any symptoms of any in the stomach. The dog was not injured by this large dose, equal to 13½ grains of phosphorus.

* Lecorche denies the caustic property of the lower oxides: Arch. de Physiol. Percy also denies it: see Trans. Am. Med. Ass., vol. 23, p. 624 and 5.

† Pages 644-647.

To make these cases parallel, it seemed to me but fair to obtain positive proof of the absorption into the blood of both phosphorus and the oxide, and as proof, I record the following experiment; but as Mr. Thompson might object to my using ol. phosph., I prepared some fresh according to his directions, and by the formula of M. Mehu,* making it of the strength of one per cent.

EXPERIMENT 5.—A young woman, aged 16 years and 5 months, was nursing her large, troublesome boy. To use her own phrase, she was "completely dragged out." She complained of being tired all the time. Sleep did not relieve her fatigue; she was hungry, but unsatisfied with what she ate. On examining her urine, I found hardly a microscopic trace of the phosphates. Her child was about four months old, with a large head and a puny, ill-nourished body; cross and irritable, sleeping but little, and constantly screaming to be at the breast.

I administered, without any change in diet, ten drops of the ol. phosph., Mehu, containing $\frac{1}{10}$ gr. of free phosphorus, three times a day, in a teaspoonful of previously-heated olive oil. She took this for three days without any complaint. After this, she complained of the usual unpleasant eructations caused by phosphorus. Both the child and herself were evidently improved. I continued this for ten days, when I was compelled to leave it off, for the toxic symptoms of phosphorus commenced to appear. During all the time, I daily examined the urine for the presence of phosphorus or the phosphates, but the increase in quantity could not be noticed. The medicine was suspended for a week, the urine remaining the same. The peculiar irritability produced by the phosphorus soon disappeared, but the same tired feeling, before complained of came on, and the boy, who had improved, was as troublesome as before.

At the end of the week I administered 4½ minims of my hypophosphorous acid, equal to about ⅓ gr. free phosphorus, at bedtime, with a little olive oil, thus making the quantity of phosphorus given daily about alike. This was administered ten days as before, with no gastric disturbance, but with a very marked improvement in both mother and child. The phosphates in the urine, though small, were distinguishable. The same dose was now given three times a day in an emulsion of olive oil, and the third day the phosphates were noticed in the urine quite plainly, and at the end of the twentieth day from commencing the hypophosphorous acid, they were quite abundant. The dose was diminished to two drops three times a day, and continued for a month with great comfort to both. Their improvement was very marked.

I think that this case is very conclusive as to the fact of the absorption of the phosphorus and of "its lower oxide." In the first place, the

* Am. Jour. Pharm. Vol. 47, p. 414.

phosphorus was absorbed, and it produced its own peculiar symptoms; to a certain extent only did it act as a nutrient. It did not, during the ten days of its administration, make its appearance in the urine, although it produced the constitutional irritation peculiar to it, and the excess, as is always the case with such doses of phosphorus, was carried off by the bowels, not by the kidneys. To some small extent it relieved the tired feeling and nervous depression of both patients, but at no time did it act as a *nutrient* or *restorative hæmatic*, as did throughout the whole month the hypophosphorous acid, which was administered in a three-fold larger dose than the phosphorus.

It is asserted by Personne,* and adopted by Thompson, that "a solution of phosphorus in hypophosphorous acid diffuses itself most easily in the blood and becomes extremely poisonous." Thompson says: "Hypophosphorous acid has been *ascertained* to add greatly to the toxic power of phosphorus." "It is, therefore, probable that the ulcerations or perforations so frequently observed in some cases of poisoning with solid phosphorus, are caused by the formation of hypophosphorous acid." "It is difficult to account for the death of a man from the single dose of $\frac{1}{8}$ grain of solid phosphorus, as in the case reported by Von Lobel, on any other hypothesis than the partial conversion of the mass into hypophosphorous acid, and the solution of the remainder in it, with the effect of producing toxic results not attainable with a similar quantity of free phosphorus."† "Devergie‡ entertains the same opinion." "It results from an observation of Martin Solon** that phosphorus exercises a much greater action when it has been transformed into hypophosphorous acid in contact with air."

In direct opposition to these remarks, Tardieu†† performed some physiological experiments, and argues the perfect harmlessness of the acid. "It has been asserted that the poisonous properties of phosphorus are owing to its conversion into phosphorous acid. It is not so. Direct experiments, conducted by us in our laboratory, have shown us that one can administer to dogs considerable quantities of alkaline phosphite, or hypophosphites, with impunity; especially in one of these experiments a dog received 12 grammes of hypophosphorous acid dissolved in water without dying, when the twentieth part of phosphorus, dissolved in this acid, and administered in the pure state, sufficed to kill it in four hours."

In "Free Phosphorus in Medicine," Mr. Thompson professes to give the bibliography on the subject; he does not, however, refer to Dr. Griscom's paper‡‡ or Dr. Percy's.§§ I would refer my reader to both of

* Gull. Gen. de Therap., 1873.
† Free Phosphorus in Medicine, p. 58–91.
‡ Med. legal, 3d ed., T. 3, p. 166.
** Dict. de Med. et de chem. prat.
†† Tardieu et Roussin Etude. Med. leg. Sur Empois, 1867, p. 432.
‡‡ Trans. Am. Med. Ass., Vol. 15. p. 183.
§§ Trans. Am. Med. Ass., Vol. 23, p. 611.

these essays. On the latter, on page 655, Percy gives a formula for just the preparation we require to thoroughly test the assertions made by Personne, Von Lobel, Devergie, Martin Solon, and accepted, unquestioned by Thompson, as quoted above; and also of numerous others who have quoted, without question, what these have stated.

These authors state, in strong terms, that phosphorus is intensified in its action, and becomes toxic by solution in hypophosphorous acid. Percy takes a solution of phosphorus in oil, and by passing dry oxygen through it for a length of time, converts it into hypophosphorous acid. I have repeated these chemical experiments or formulæ, and have satisfied myself that the phosphorus in solution, in the oil, is converted into an acid of that element. We could not then have a better material to thoroughly test the questions in issue, because the acid hypophosphite is in exactly the condition that Thompson says it arrives at after absorption. This oleo-hypophosphite of Percy's can be readily improved, both in taste, smell and method of manufacture, and before proceeding with this discussion I would suggest what I think an improvement. Instead of passing oxygen gas through the ol. phosph. as Percy has done, and allow a large quantity to escape and be lost, I would proceed in the following manner:

Preparing the oil and dissolving the phosphorus in the manner described on page 655, instead of passing oxygen through the oil, I put it into a stout syphon bottle, and for every cubic inch the bottle holds I pass in, under pressure, two cubic inches of dry oxygen gas. The oil can then be well agitated for any length of time, and if the desired changes are not completed at once, it can be left for a more convenient time. The method proposed saves the necessity of constant watching, and the product is better. Upon letting out the oxygen, it is found to be converted into ozone, as it discolors the test paper. Upon agitating this oil with warm water, drawing off the water and filtering it, chemical tests prove the presence of hypophosphorous acid.

We see then that although Percy has succeeded, and was the first to form an anhydrous hypophosphorous acid and hypophosphite, it is not stable in the presence of water, the acid leaving its combination with the oil and clinging to its old affinity.

EXPERIMENT 6.—Taking three dogs as nearly as possible in the same condition, I commenced treating them in the following manner: to

A. I gave ol. phosph., Mehu. $\frac{1}{10}$ grain at a dose.

B. I gave Percy's anhydrous oleo-hypophosphite, equal to $\frac{1}{10}$ grain of phosphorus.

C. I gave ol. phosph. and oleo-hypophosphite equal quantities, but making the whole $\frac{1}{10}$ grain of phosphorus at a dose.

As my object was to see the different therapeutic and toxic action of the medicines, I omitted all minor considerations, such as a constant watchfulness of the pulse, the temperature, etc., etc.,

I commenced giving to each a dose equal to $\frac{1}{10}$ grain of free phosphorus at 8 and 11 A. M. and 3 and 7 P. M. They were allowed to run round the room, and water was allowed them to drink. For the first 48 hours no difference was noted; at 58 hours A. was dejected, the cornea were congested, and he was constantly straining to urinate, but the urine was passed in very small quantities, and in such a manner that it could not be saved; the pulse and temperature were both increased. At 72 hours, A. was in about the same condition, B. and C. were in perfect health. At 96 hours, A. was very dejected, would eat no food when it was offered him, and would not rise unless driven up; the pulse was slower, respiration less frequent, the temperature two degrees higher; B. and C. ate heartily and were playful. At 120 hours, the dose having been continued to each four times a day, all the dogs seemed in about the same condition as yesterday, A. had eaten nothing. At 144 hours, A. was much prostrated, the pulse was thready and very rapid, the respiration was short and quick, the temperature was five degrees higher than normal. At 147 hours, he died without convulsions or spasms. A post mortem examination was made immediately: The intestines were nearly empty; there were two large hæmatomata on the mucus membrane of the stomach; the liver was soft and of a dark color, it was wholly disorganized by fatty degeneration, there was a large hæmatomata upon the upper border; the heart and kidneys were disorganized by fatty degeneration. In short, the dog died with all the symptoms of phosphorus poison, and all the proofs of such poisoning were found upon examination.

The medicine was continued to B. and C. until the 168th hour, when it was discontinued; they were both in good health.

I have stated that the liver of this dog A. was soft and of dark color, and disorganized by fatty degeneration; the gall bladder was filled to distention with bile, which was poured into a glass and examined. It was of a brownish-yellow color. About two drams of it were mixed with double the quantity of distilled water, and a little of it put into a test tube; on the application of heat it became much clearer and more transparent, but on the continued application of heat, a large floculent deposit separated, showing the probable presence of both urea and albumen. To test this more thoroughly, some of this diluted bile was filtered into a test tube, and a little acetic acid added, it was then boiled and a large deposit took place, nitric acid was added which did not dissolve the precipitate, thus proving the presence of urea and albumen.

By applying Day's test,* *urea* was proved to exist in large quantities. *Albumen and urea are not constituents of healthy bile.* We produced in this dog *Bright's disease,* fatty degeneration, and, as a consequence, we find *albumen and urea* in the excretions.

The kidneys were found, on microscopic examination, to be in a state of fatty degeneration; they were unable to perform their functions; *urea was therefore retained in the system and found in the bile.* A small quantity of urine was found in the bladder; it was *loaded with albumen.* The animal died from *phosphorus poisoning, i. e.,* acute BRIGHT'S DISEASE, and its sequel *uræmic poisoning.*

The whole liver of this dog was treated by the directions given by Attfield,† to ascertain if any free phosphorus existed in it, but although it had the strong peculiar phosphorus smell, I failed to detect any phosphorus by the tests.

In these cases, *if* Mr. Thompson's *theory* was correct, C. should have been much more quickly poisoned than A., but as he took only half the dose of phosphorus, and the other half was a hypophosphite, the phosphorus was not sufficient to poison him, and the hypophosphite probably acted as a nutrient. At any rate, we see in these cases that Mr. Thompson's *theory,* "that phosphorus is intensified in its action and made toxic by union with hypophosphorous acid," is a mere assertion and at variance with facts. The experiments of Churchill and the large number of physicians who followed his practice and gave the hypophosphites, are recorded, they pass as additional proof with the experiments I have given here.

We also see by these, and previous experiments before related "that the ulcerations, or perforations, so frequently observed in cases of poisoning with phosphorus, are caused by the formation of hypophosphorus acid," is not correct, but that these hæmotomata are due to the action of phosphorus alone, and are nearly always present in a case of poisoning with that element.

In the only recorded case of poisoning with hypophosphites that I have seen, there were no such spots to be found.‡

EXPERIMENT 7.—At the expiration of two weeks I gave to the dog B. ol. phosph., made into an emulsion with hypophosphorous acid added to it. It was given as before, four times a day, each dose containing $\frac{1}{10}$ grain of free phosphorus and one grain of hypophosphorous acid. It was given four times a day for 6 days. At the expiration of that time the dog was not in the least injured by it.

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*Day's Physiological Chemistry, p. 41.

† Attfield's Chemistry.

‡ Trans. Am. Med. Ass., Vol. 23, p. 647.

I directed four medical students to perform the following experiments; I give the results in their own language:

EXPERIMENT 8.—"Report of an experiment, ordered by Professor ——, made with $\frac{1}{10}$ grain of phosphorus, dissolved in beef suet, administered three times a day, from Nov. 17 to Dec. 6, to a brindle dog, about 18 months old. Temperature taken morning and evening:

"Nov.	17th,	9 A. M.,	98⅔	"Nov.	27th,	9 A. M.,	100⅓
		6 P. M.,	99⅓			6 P. M.,	102
	18,	9 A. M.,	100		28,	9 A. M.,	101⅓
		6 P. M.,	100			6 P. M.,	102
	19,	9 A. M.,	101⅓		30,	9 A. M.,	104⅔
		6 P. M.,	101⅔			6 P. M.,	103⅔
	20,	9 A. M.,	101⅓	Dec.	1,	9 A. M.,	102⅓
		6 P. M.,	101⅓			6 P. M.,	102⅓
	21,	9 A. M.,	101⅔		2,	9 A. M.,	102⅓
		6 P. M.,	102			6 P. M.,	103⅔
	22,	9 A. M.,	101⅓		3,	9 A. M.,	105
		6 P. M.,	102⅓			6 P. M.,	105⅓
	23,	9 A. M.,	102		4,	9 A. M.,	101⅔
		6 P. M.,	101⅔			6 P. M.,	101⅔
	24,	9 A. M.,	102⅓		5,	9 A. M.,	99⅔
		6 P. M.,	102⅓			6 P. M.,	98⅓
	26,	9 A. M.,	102				
		6 P. M.,	100⅓				

"Dec. 6th, made post-mortem. The whole left side of the thorax presented one large ecchymosis, over which the hairs were easily pulled out; the ecchymosis extended through the muscles and between the ribs to the pleuro-costalis; and on three large spots the pleuro-pulmonalis was involved. Upon the middle lobe of the right lung were several small ecchymosed spots, and also upon the right ventricle of the heart. The lungs, instead of being pinkish-white, were of a dirty yellow-red color; they did not crepitate upon being handled; they were quite oily. Upon examination under the microscope, the parenchyma, the air cells, in fact the whole structure was infiltrated with oily drops; some of the air cells were completely filled with oil; the whole lung structure was disintegrated. The muscular structure of the heart was much infiltrated. The aorta, upon its inner surface, was plastered over with a pasty mass, which upon microscopic examination, was found to be disintegrated blood, mixed with oil globules. Upon the liver were several small ecchymosed spots; the whole organ was so disintegrated with oily infiltration that the structure could not be discerned with the microscope. The bladder was distended to a large size with urine, which was oily and

highly albuminous. The lower intestines were filled with fæces, very tenacious and black as pitch, which, upon microscopic examination was found to consist of some muscular fibre, mixed with some broken-down blood discs and oil globules; the blood was an exudation from ecchymoses in the upper intestines. The kidneys were soft and doughy; they had an oily appearance, and upon microscopic examination were found to be so completely broken down by oily infiltration, that their structure could not be studied."

EXPERIMENT 9.—During the time that the dog, just spoken of, was being watched, two other students administered, in an oily emulsion, twelve grains of the hypophosphorous acid before described, being equal to 4½ *grains* of "free phosphorus," daily. They report: "According to your directions, we discontinued all medicine to this dog on the death of the brindle dog. He seems quite well, and has a good appetite."

EXPERIMENT 10.—During the same time a smaller black dog was fed with $\frac{1}{10}$ grain of free phosphorus in exactly the same manner as the brindle dog, but he was made to inhale oxygen twice a day, and was given oxygenated water ten minutes after each dose.

They report to me: "The dog is still alive and in tolerably good health; he will be watched for some time."

Three months have elapsed, and both the dogs 9 and 10 are in good health.

We thus see, by these experiments, that 5 *grains* of "free phosphorus" administered to a dog, in 17 days destroyed him, producing *acute Bright's disease;* that another dog treated in like manner with the same dose, and for the same time was saved by Percy's antidote, Thompson's much dreaded *oxygen*—and that another took 204 *grains of hypophosphorous acid,* equal to 76½ *grains of phosphorus,* with no furher injury than depression of spirits and irritability.

EXPERIMENT 11.—A young man suffering from the effects of self-abuse was given 10 drops of my hypophosphorous acid three times a day in syrup. Before commencing the medicine the urine was tested to ascertain the quantity of phosphates present. The urine was pale, large in quantity, sp. gr. 1.012, and upon using the tests a very small quantity of phosphates were detected. The acid was continued a week when another examination was made, then the whole urine of the previous 24 hours was saved, and found to amount to 34 ounces: a measured quantity of this was tested, and 21 graines of phosphoric acid was found. From abstinence of a bad habit, a more nutritious diet, and the medicine, the patient was very much improved. The medicine was continued for

another week, and the same examination of the urine then made and the phosphoric acid was found to amount to 27 grains. Five drops of hypophosphorous acid with 3 grains hypophosphite of iron was then given three times a day, with continued improvement, especially in the symptoms of nervous timidity. In a week the urine was examined, and the phosphoric acid was found to amount to 26 grains. He was a little alarmed, and told me that his "stools were black," good evidence of the action of the iron, and proof of the proper absorption of the hypophosphites.

While carefully watched this young man recovered rapidly, but after awhile watchfulness ceased, and he returned to his habit. I cured him only at last by snipping off with a scissors a small thin edge of the prepuce, often enough to keep the organ constantly sore. This practice I have pursued many times with the greatest benefit, in one case lasting over two years.

On page 45 of Thompson's "Free Phosphorus in Medicine," the author says: "The phosphorus to be reduced is placed in a long, narrow vessel with water of a temperature to melt it: on violent agitation it is reduced to globules of great minuteness, and the rapid cooling of the water employed by the sudden addition of a large quantity of cold water, solidifiies these particles while they are yet suspended, and permits them to fall together at the bottom of the vessel without cohering. By this process a white powder is produced, which consists of particles of phosphorus, of which each is coated with *phosphoric acid.*' 'Eventually phosphorus (when placed in water) becomes coated with *phosphoric acid, by which further change is prevented,* and even its inflammability is diminished.' 'The ultimate result of the prolonged immersion of phosphorus in water is its oxidation, *i.e., its conversion into phosphoric acid;* but before reaching this point it forms phosphoretted hydrogen, and it passes through the lower stages of oxidation, becoming hypophosphorous, phosphorous acid, phosphoric acids successively.'

'In the first of these oxides free phosphorus is soluble, and to a small and ever-changing proportion of the metalloid is always in solution in the water in contact with it, and in a form which, as in the case of olive oil solutions, is well calculated to intensify its activity as a poison.'"*

If this "white powder" is examined by a magnifying glass it will be found to consist of minute globules of phosphorus, which are white because they are so intimately divided. If after they have settled the bottle is warmed to 100° F., they will all again unite into a single mass, and will be easily recognized as ordinary phosphorus.

Weigh 10 grains very accurately, and treat it in the manner directed by Thompson, and let it stand at rest for a day; then heat the bottle,

* Pages 3, 5.

and carefully bring the whole into a single globule; weigh this accurately, and the finest balance will hardly detect a loss in weight.

Mr. Thompson's chemistry seems to be as bad as his therapeutics. He does not seem to be aware of what the earliest student of chemistry knows, that phosphoric acid is exceedingly soluble in water, and has such intense affinity for that fluid, that it deprives even sulphuric acid of its water. It is soluble in all the fluids of the body, and could not exist as a coating to phosphorus in th epresence of fluid for an instant. Phosphorus which remains in water, becomes coated with a yellow, a red, or a white covering, which is not *phosphoric acid*, or any of the soluble oxides of phosphorus, but is mostly amorphous phosphorus. This has been proved by Graham, Richardson and Watts, Fowne, Shrotter, Percy and others.

I have, to-day, examined the water from a four ounce bottle which has contained three sticks of phosphorus for about two years; the sticks being now thickly coated with amorphous phosphorus. With the reagents chloride of barium, acetate of lead, chloride of mercury, chloride of calcium, sulphate of copper, I do not find any hypophosphorous acid, although according to Thompson "it contains an ever-changing portion," and with the use of molybdate of ammonia and hydrochloric acid, the amount of phosphoric acid in solution is so small as to make its detection almost microscopic.

Therapeutics, like chemistry, must become a science of facts, or we descend to mere empiricism.

Phosphorus and its compounds being very largely used in medicine, the points I have here discussed are of the very gravest importance.

I have stated that there is danger in administering "free phosphorus," of producing nephria or nephritis. I have not made this observation without due attention to the subject. It will be remembered that I have, in this Essay, quoted several cases of poisoning with phosphorus, observed by others and by myself. By reference to these it will be noted that in every case there was fatty degeneration of the kidneys. I have instituted a series of experiments for the express purpose of examining the condition of the kidneys of smaller animals, to which phosphorus was administered.

EXPERIMENT 12.—To a kitten about three months old, oleum phosphor. (Mehu) amounting to one-twentieth grain of phosphorus was administered three times a day. The ordinary symptoms of acute poisoning was seen, and on the seventh day the kitten died.

Upon post-mortem examination, the left kidney, which was larger than the right, was of softer consistence than natural. An ecchymosed spot occupied the upper portion of the internal border. Upon making a

vertical section of the organ, the pelvis was found to be in the same condition. Both cortical and medullary substances were infiltrated with oil. A section, under the microscope, showed the inner surface of the veins plastered over with this albumenoid oily substance. The right kidney was not so far advanced in disease as the left, but was beyond the power of functional activity.

EXPERIMENT 13.—To a kitten of the same age as the last, $\frac{1}{30}$ gr. of phosphorus was administered three times a day. On the eighth day of this treatment it was killed instantaneously. The kidneys were examined, both by the unaided eye and by the microscope. They both showed, quite plainly, fatty degeneration.

EXPERIMENT 14.—To a small dog, $\frac{1}{30}$ grain of phosphorus was administered three times a day for twenty-three days. It was then suspended for seventeen days. He was killed, and the kidneys, the heart, the liver, and the whole muscular structure was disorganized by fatty infiltration. The dog became very dejected and morose after the fourteenth day, and he did not recover his spirits after the phosphorus was suspended.

EXPERIMENT 15.—A rat was caught, in a trap, that had eaten phosphorus paste. It was put in a cage and supplied with water and food. It ate and drank sparingly, but did not recover its animation. After a week its hair almost all came off. Broth thickened with oatmeal was given it to eat. It had frequent attacks of cholic pains. On the nineteenth day it died in a convulsion. On the mucus membrane of the stomach were three hæmatomatic spots, and on the different portions of the intestinal tract were seven of these spots. The kidneys were oily and soft as putty.

Dr. C. J. R. Williams* says: "In two cases of paraplegia where I gave phosphoretted oil in very small doses, in a few days it produced jaundice, with tenderness and enlargement of the liver. No such effects followed the use of the hypophosphite."

Dr. Thorowgood† says: "The oil in so small a dose as 10 drops of a solution of [illegible] grains of phosphorus in one ounce of olive oil ($\frac{1}{24}$ of a grain) is very nauseous to the stomach, gives a lucifermatch-like smell to the breath, and if persisted in causes jaundice, and sometimes serious hepatic derangement. It is, therefore, a troublesome and unsatisfactory medicine, and I have [illegible] ceased to use it in practice for some years."

Dr. [illegible] has used "free phosphorus" against consumption, [illegible] but without success.‡ Dr. [illegible] has used it with no better [illegible]

* Williams on Pulmonary Consumption, p. [illegible]

† Thorowgood on Consumption, p. [illegible]

‡ [illegible] on Consumption

§ British Med. Jour., 1867, p. [illegible]

Dr. George Wegner, of Berlin, has published some important researches on the deleterious action of phosphorus. in Virchow's Archiv'. "Its most remarkable effect, when taken for some time, is the production of fatty degeneration of the liver, kidneys, stomach and heart; and at a later period, the establishment of a similar condition in the voluntary muscular system generally, in the unstriated muscular tissues of the intestines, and even in the lungs. Numerous hæmorrhages occur in all parts of the body, owing to an extension of fatty degeneration from the heart to the entire arterial system.

Churchill says (p. 342): "While phosphorus is a highly dangerous and uncertain medical agent, the hypophosphites are a real *nutriment*. Not only may they be given in large doses without any poisonous effect, but they can be injurious only in case their physiological action is perseveringly kept up beyond due limits, just as happens with any other of the natural elements of the organism. When the hypophosphites are given in excess, the surplus of what is worked up in the system is excreted by the urine."

By request, Dr. Arnold has sent me the following letter: "On 16th of January, I was asked to see two young leopards affected with rachitis. They were about 3 months old, could not walk, but dragged themselves a short distance about the cage on their bellies; their teeth were not developed as usual with such animals. I began the administration of hypophosphite of lime, 20 grains daily in their meat. They began to improve after the first week, and the smaller one improved much more rapidly than its larger brother. The dose was increased to 30 grains daily, with steady improvement in strength, weight and activity."

"Free Phosphorus in Medicine," is the first large work in English on the subject, though there are many smaller ones, and many short articles in the journals; it contains many errors, and we know that it is of more importance to correct an error than to promulgate a new idea. In a scientific spirit I have endeavored to learn the truth, and I present chemical tests, post-mortem examinations, therapeutic experiments and physiological investigations to speak for themselves. I hope to prevent the fearful destruction of life that must result if Thompson's unfounded assertions go uncorrected.

Free phosphorus, as a medicine, has been administered in many vehicals, in olive oil, almond oil, cod-liver oil, in either, alcohol, bi-sulphide of carbon, chloroform, glycerine, etc., etc.

It has been given also in the solid fats of animals; was recommended by Percy in the pill form in cocoa butter; it has lately been made into pill form with wax, spermaceti, resin, balsam of tolu, paraffin, soap and other things.

To-day the market is flooded with "Phosphorus Pills;" they are the latest sensation of the profession. Fortunately, many of them are totally inert, the modicum of phosphorus they contain having been converted into phosphoric acid by the imperfect method of manufacture. If made with the solid fats and immediately coated, as directed by Percy, they contain essentially the same substance as ol. phosph., *i.e.*, phosphorus in solution. But many of these pills are made by persons misunderstanding the physiology of digestion, and wax, resin, paraffin and other things of which they are compounded, are not digested in the stomach, and the pills are consequently passed as whole as they were taken.

Mr. Walling* and Dr Frowert* have made careful experiments, and report some of these pills passed 10 and 18 hours after they were taken entirely unacted on. These reports are very able, and well worth a careful perusal.

In what state do we find the phosphatic compounds in the tissues of animals and plants? Schmidt has found in 8.55 parts of the solid residue of the saliva, 1.16 of phosphate of lime, and magnesia.

In the gastric juice he found 2.090.

In the pancreatic fluid, 0.54.

In the blood, 163.33 solid parts yielded 1.706 of phosphates.

In the ash of hens' eggs, 70 per cent of phosphoric acid.

In the ash of milk, 28.04 per cent of phosphoric acid.

In the urine, in varied proportions, according to the kind of food used.

In the cartilaginous tissues, he found it as phosphate of lime and magnesia.

In the muscular tissue, as ortho-phosphoric acid in combination with lime and potash.

In the ash of the liver, 43 per cent was phosphoric acid.

In the ash of the brain, 93.57 per cent. consists of phosphates.

Schmidt, Day, Lehman, Liebig, and numerous other chemists, have found it in every part of the human frame, but no one has made any claim to have found it as "free phosphorus;" they have found it as one of the acids of phosphorus combined with an alkaline base.

Fremy and other French chemists found it in the brain in a peculiar form, and called it "oleo-acid-phosphorique."

Later, Germen and French chemists have found the soluble phosphates in the vegetables we eat, and Percy in his essay mentions them in varied and interesting combinations both in vegetable and animal structure.

The phosphates are daily needed in the system, and they are needed to a large extent. Lehman while living on an animal diet excreted

* Am. Jour. Pharm., Vol. 47, pp. 258-84.

54.52 grains daily; no one will contend that this was or could be supplied in the form of "free phosphorus," and no one but Thompson and a few other thoughtless investigators will deny that that amount could be taken "with the greatest safety" either as the medicinal hypophosphites, phosphites or phosphates. It has become a very common practice for many to recommend "free phosphorus," either in solution, or the later fashionable novelty, pills, for the purpose of restoring the lost element to the system, or of restoring function to weakened nerves. It is recommended in the maxium dose of $\frac{1}{10}$ grain, but more frequently in $\frac{1}{30}$ grain doses three times a day. We have above shown a loss of 54.52 grains daily: here is an attempt to supply that loss with $\frac{3}{10}$ of a grain.*

So far then as any restorative or nutrient action is concerned, we must leave "free phosphorus" out of consideration. We have seen by all the experimental cases that we have brought forward, that it did not in any of them become converted into any of the nutrient oxides, but continued its own poisonous and innutritious effects unchanged until it destroyed the victim. Even in this small dose of $\frac{3}{10}$ grain daily, it cannot be taken for many days without producing most alarming symptoms, and without tending strongly to induce a fatal disease which no after treatment will cure.

We see in all the cases I have here related, in all the post-mortems that are described, BRIGHT'S DISEASE, fatty degeneration of the tissues and organs, numerous hæmatomatæ, with the presence of albumen in the urine, and albumen and urea in the bile. This remark holds good equally with those that have been poisoned with large and overwhelming doses, and with those to which small and repeated doses were given. Even in minute doses, and where its action has been suspended for a long time, no oxidation of the phosphorus has taken place, and upon killing the animals, *chronic Bright's Disease*, was found to have been produced.

Can we be too careful how we sanction the indiscriminate use of such a medicine.

I have before pointed out that some writers on phosphorus have made an effort to prove that it owes its dangerous properties to its action of absorbing oxygen from the tissues.

Think for a moment of the dose usually given, let us say the maximum $\frac{1}{10}$ of a grain, how large a dose of oxygen would it take to saturate it, supposing it capable of being saturated? How insignificant the withdrawal of this modicum of oxygen would be, and how small an effect on organs that are always supplied with oxygen in abundance.

* "Beyond this immediate power (of stimulating the nerves) there seems no reason to doubt that phosphorus, taken in small repeated doses, may supply the nerve matter with those phosphatic compounds which are wanting. Phosphorus is a nerve stimulant, and more than this, a nerve food."—*Thompson's "Free Phosphorus in Medicine."*

At the same time that these authors tell us that the phosphorus becomes poisonous by withdrawal of oxygen from the tissues, they tell us that this withdrawal causes disintegration. If the oxygen is withdrawn in the instance they quote, it must have saturated the phosphorus and converted it into a harmless compound, phosphoric acid. The action of the phosphorus should then cease. The poisonous action of phosphorus seems, however, not to cease, and we have proved that it does not absorb oxygen from the tissues, for in the experiments I have quoted, the toxic action continued from the first full dose until death.

Dr. Broadbent has stated that phosphorus and arsenic are similar in their action.

There is no doubt with the numerous closely related cases before us, and their post-mortem appearances, that phosphorus has an action entirely dissimilar to any of its compounds: it is absorbed in its entirety, and remains in the system for many hours, producing its effects without undergoing oxidation or other change. The effects that it produces are peculiar to itself, and unlike any other medicine that we know. That it continues to act as phosphorus, and not as any of its oxides, is readily proven by the peculiar odor it gives the breath and the odor that is present even ofter death. Statements have been made that such bodies are luminous after death. Phosphoric odor and luminosity belong only to phosphorus, and not to any of its acids.

On the other hand, some who have pretended to copy Churchill with his hypophosphites, and hosts of others who have used the various phosphates, have claimed too much for these oxides of phosphorus; they have been given for almost every disease, and all the benefits that have been derived from change of air or occupation, or other therapeutic remedies, have been claimed wholly for their favorite preparation.

Churchill's book on Consumption is so full of reports of cases, treated both by himself and a great number of other physicians, with the hypophosphites, that I need but refer to these reported cases. We see amongst them but few where the hypophosphites were given in dangerous doses, and with such a record and with such names of celebrity it is hard to see how Thompson could make the assertions he has. Thompson's book has done much, yes, nearly all, to force upon us our latest sensation "phosphorus pills," for there are numbers in our profession no better skilled in chemistry and therapeutics than he. Let us hope that this latest fashionable folly will not result in multiplying our cases of Bright's disease,

The force and earnestness of argument on the two sides of this question must be given with different emphasis. In discussing the use of "free phosphorus," we are considering a most active agent; one from which a patient seldom recovers where it produces its toxic action; and one which, if long continued in small doses, may lay the foundtion for

chronic albumenuria and uræmic poisoning. With the oxides of phosphorus, on the other hand, we have but few causes of danger to apprehend.* The one oxide is so easily and frequently, in its passage through the body, converted into the other oxide,† according to whether it is receiving or giving oxygen, that we have but little danger in any moderate dose. It is also so exceedingly soluble, and so readily unites with the alkaline bases in the system, that its excess is soon passed off either by the kidneys or bowels. We must not forget, also, that the oxides of phosphorus exist as component parts of vegetables and all foods that we eat.

Every proof that we have is against the oxidation or assimilation of phosphorus. When once absorbed into the system, it there remains as phosphorus until expelled *by the bowels;* it takes no part as a nutrient; its action is simply that of a medicine, and occasionally a good and useful one.

I have been asked, Is the action of phosphorus on dogs similar to that on man?

Similar, but different in degree! A man, with his susceptible nervous system, will not bear the same proportionate dose as a dog. The effects upon the organs are similar; they but differ in degree.

Upon consulting the "Table of Mortality" of the Health Department of the city of New York, I find that the number of deaths from diseases of the kidneys, for the year 1874 was 975; the number of deaths for 1875 was 1108—138 more than the previous year. Is this increase due to the use of phosphorus pills?

The sale of Dr. Thompson's book, "Free Phosphorus in Medicine," is probably due, in a great degree, to the prestage it received from its dedication to Dr. C. Murchison. I have in this Essay confined myself principally to the correction of Dr. Thompson's errors in the Chemistry of phosphorus and its compounds. As so many of our medical men are not conversant with chemistry, and are looking for all improvements in therapeutics. they take for facts these ill-based theories of Dr. Thompson on the action of phosphorus. I am sorry to say that the relation of his "cases" could be subjected to a severer criticism than his chemistry, and that his whole book may lead to serious and oft-times fatal results.

I thus leave open to the discussion of the Profession this "Chapter on *Experimental Therapeutics.*"

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* Tardeau gave 186 grains of hypophosphorous acid at one dose without dangerous results.

† I have given hypophosphorous acid to a dog, and detected free phosphoric acid in both the saliva and urine.

NOTE.—I need hardly remind my professional brethren that this Essay was offered to the State Medical Society in competition for their prize; as such it was necessary that the author should not be known; I had, therefore, to use my own name frequently, as there have been but few investigators on this subject. I leave it as it was written.—*S. R. Percy*

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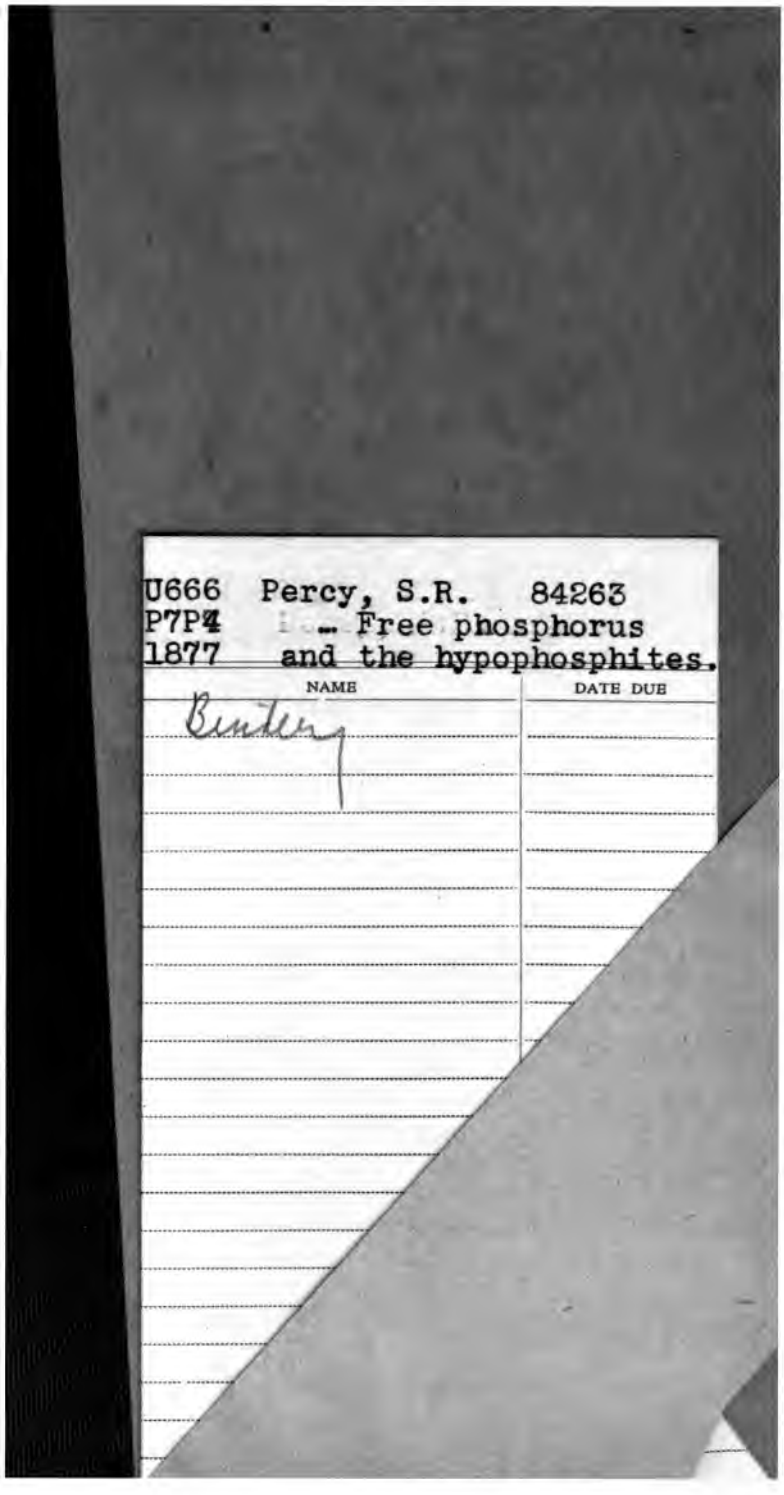

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